Arthur Schatzkin
Surrogate Markers Workshop
December 98

Surrogate Markers Workshop: Presentation

1. Title: **Limitations of Surrogate End Points in Cancer Prevention Research**

   Raise some practical and theoretical problems that we've encountered in using surrogate endpoints in various cancer prevention studies.

2. Cartoon: Ulrich, that's bad science and you know it.

   Trick is to figure out when using surrogates is good science--and when it's bad.

3. Schematic of cancer: exposure--->internal dose--->biologically effective dose--->early biologic effect--->altered structure/function--->cancer

4. Many chronic diseases occur relatively infrequently:
   breast cancer: 100/100,000
   colorectal cancer: 50/100,000

5. Therefore intervention studies with cancer end points tend to be big, long, and costly.

   E..g., WHI, requiring several tens of thousands of participants to have adequate power to detect reasonable reductions in incidene of breast and colorectal cancer.

6. Studies with surrogate end point markers can be smaller, shorter, cheaper.

7. **Definition of a Surrogate End Point for Cancer**

- In an intervention study, a surrogate end point for cancer yields a valid test of the null hypothesis of no association between the intervention and cancer.
- In other words, the surrogate gives you the right answer about cancer.

8. Broad range of possible surrogate endpoint markers (1)

There are a whole host of biologic phenomena, biomarkers, that could potentially serve as disease surrogates, and with the explosion in molecular and cell biology, this list is only growing. Here you see potential surrogates, all of which have been used or proposed as surrogates in studies, lumped for the sake of convenience into a set of categories:

Changes in the microscopic or gross characteristics of tissues: includes colorectal adenomas (polyps) for colorectal cancer, cervical intraepithelial neoplasia (CIN) for cervical carcinoma, bronchial metaplasia (a possible pre-neoplastic state) in lung cancer, and dysplastic changes in the esophagus.

Interest in various imaging techniques to detect histologic change. Includes mammographic parenchymal patterns as a surrogate for breast carcinogenesis, and ovarian ultrasound abnormalities in ovarian cancer.

Cellular phenomena. Includes various indices of epithelial cell proliferation, including tritiated thymidine, bromodeoxuridine, PCNA, Ki67 assays. Measures of apoptosis have recently been proposed as potential surrogate endpoints. And in AIDs research, CD4 cell counts have been used as surrogates for critical AIDS endpoints.

9. Broad range of markers (2)

A plethora of molecular markers have been suggested. For example, specific somatic mutations like ras and others. DNA hypomethylation as a key factor in carcinogenesis. Here, as I mentioned earlier, are chemical-DNA adducts as indicators not only of exposure but of an integrated metabolic process that is further downstream from the exposure itself.

Infectious processes have been implicated in a number of cancers, and these infectious could serve as surrogates. Examples include human papillomavirus in cervical carcinogenesis or Helicobacter pylori in gastric cancer.

And finally there are the myriad substances found in blood and tissue that have been considered as possible surrogates, including such things as blood and tissue estrogens or androgens, growth factors, auto-antibodies to DNA. What's interesting here is that the marker may not be found directly in the target tissue, as in blood estrogen levels vis-a-vis breast cancer, but may still properly be considered a potential surrogate endpoint.

10. Picture of colorectal cancer

11. **2 Potential Surrogate Endpoints for Colorectal Cancer**

- Epithelial cell hyperproliferation
- Adenoma recurrence

12. Picture of crypt with PCNA-labeled cells

13. Schematic of proliferation: labeled cells within idealized crypt

14. normal-->hyperproliferation--->early ---------->late------> invasive
epithelium adenoma adenoma
cancer

This shows where hyperproliferation fits into carcinogenesis--this reflects a single pathway.

15. Same proliferation scheme, but with additional, alternative pathway through apoptosis, etc.

Interest in creating computer models of disease processes. Would require knowing all these pathways and their relations to one another so could predict effect of an intervention somewhere in the process.

16. **Proliferation Markers as Surrogate End Points for Colorectal Cancer: Inferences (1)**

- Hyperproliferation may not be necessary for CRC; that is, there may be an alternative pathway bypassing hyperproliferation.
- The effect of an intervention agent on the alternative pathway may counterbalance the effect on the hyperproliferation pathway.

17. **Proliferation Markers as Surrogate End Points for Colorectal Cancer: Inferences (2)**

- Hyperproliferation may give the wrong answer about an intervention agent's effect on CRC

  - Agent reduces proliferation, reduces apoptosis, has no effect on CRC

  - Agent has no effect on proliferation, increases apoptosis, reduces CRC

[Emphasize: proliferation marker *may* give the wrong answer, but it may give the *right* answer. There's uncertainty a priori. NB: this is change from earlier writings: the marker's being a necessary component of pathway to cancer is no longer necessary for surrogate to be 'valid'--you could have an alternative pathway that does not offset the primary pathway. It's just that, in absence of data on all this, the 'necessary' marker is a much safer bet--when alternative pathway is weak or non-existent, i.e., when attributable proportion is close to 1.0, then we can feel confident in this surrogate a priori.]

18. **Hyperproliferation as a Surrogate End Point for Colorectal Cancer: How Do We Obtain Data to Evaluate These (Theoretical) Inferential Possibilities?**

19. **Answer: Integrate Proliferation Markers in Colorectal Neoplasia/Cancer Trials**

[Mention that integration into observational studies can also be informative. Also mention that can integrate markers into animal studies, such that have a complete model: carcinogen exposure and possible modulation, surrogate, cancer. Because of commonalities of protoplasm and carcinogenesis, may be informative with regard to surrogate.]

20. **Integrating Proliferation Markers in Trials: 3 Questions**

[Again, mention this holds for observational studies, too.]

- Does the proliferation marker predict cancer/neoplasia?
- Does the intervention affect proliferation?
- Does the proliferation marker mediate the effect of the intervention on cancer/neoplasia?

'Mediation' is a rather loose term. Some of the articles provided for us give a more rigorous mathematical treatment of this, suggesting strengths and weaknesses of different parameters reflecting this concept.

21. Irony of surrogate end point marker validation

To get evidence that proliferation indices (proliferation/apoptosis) is valid surrogate for CRC, have to include in studies with cancer or neoplasia endpoints--and that's the study you were trying to avoid

22. **If we demonstrate that hyperproliferation is a good colorectal cancer surrogate in one trial (with a given intervention), can we use hyperproliferation as a cancer surrogate in trials with other interventions?**
23. Schematic with 2 agents and 2 markers:

Agent 1 goes through surrogate and other marker on way to cancer
Agent 2 goes through other marker and surrogate on way to cancer.
Even if agent 1 is a good surrogate, such that pathway through other marker does not offset pathway through surrogate, can't say same for agent 2.

24. **Intervention Agent Specificity?**

- Can we ever be certain that 2 different intervention agents have pathophysiologic effects so similar that if hyperproliferation is a valid CRC surrogate for one agent it must be for the other?
- That is, can we ever avoid worrying that the second agent has some unanticipated effect on an (unknown?) alternative pathway?

It's been suggested that surrogacy is transferrable among closely related agents, i.e., a class of pharmacologic compounds. Maybe, but remember that drug companies spend big bucks tweaking compounds, adding or subtracting a methyl group here and there, to reduce adverse effects--could go in opposite direction as well.

25. **Statistical Considerations: 'Noise' in Proliferation Markers (1)**

- There is substantial variability ('noise') in proliferation assays, with several sources of within-participant variation (e.g., over time, between biopsies, reading-to-reading).
- 'Signal-to-noise' ratio may be problematic: is it possible to discriminate among participants given substantial within-participant variation?

26. **Statistical Considerations: 'Noise' in Proliferation Markers (2)**

- May be possible to decrease within-participant variation (e.g., via increased biopsies).
- Information on variance components is critical.
- Such data are sparse (estradiol, proliferation)
- Measurement error will attenuate associations (e.g., between marker and cancer).

27. **Summary: Hyperproliferation as Surrogate End Point for Colorectal Cancer**

- It's unclear whether hyperproliferation is a valid CRC surrogate for *any* (let alone all) intervention agents.
- Note: a combined proliferation-apoptosis index could be informative. But problems of interpretation don't go away.

28. Picture of adenomas (polyps) in large bowel segment

29. Picture of adenoma-carcinoma sequence

30. **Rationale for Adenomas as Surrogate End Points for Colorectal Cancer**

- Adenoma-carcinoma sequence
- High prevalence (but only 5-10% screenees randomized)
- High recurrence rate (2 orders of magnitude > cancer)
- End point assessment via standard clinical practice

[31. Overhead]

Calcium and Colorectal Cancer Surrogates: Polyps and Proliferation

Adenoma Recurrence Trials

Investigator(s)	Intervention	N	Results
Baron/US	**calcium carbonate (3 g; 1200 mg ca++)**	**930**	**↓AR (1+, ↓17%; #, ↓25%)**
ECP/Europe, Israel	calcium 2g/d; (also fiber supplement)	~800	Ongoing (AR and progression)
WHI/US	calcium (1000 mg/d) + vitamin D (400 IUs/d); in 3x2x2 with hormones, diet	67,000 ♀; (45,000 in CaD)	Ongoing (CA)

Colorectal Epithelial Cell Proliferation Study

(Baron et al.)

	PCNA labeling index (s.e.)	Brdu labeling index (s.e.)
calcium group	3.85% (0.08%)	3.88% (0.30%)
placebo group	3.92% (0.08%)	3.54% (0.21%)
	P=0.30	P=0.54

There was no group difference in intra-crypt distribution of labeled cells.

32. **Adenoma Recurrence as Surrogate End Point: Caveats in Generalizing to Colorectal Cancer**

- Flat dysplasia pathway
- Early neoplastic change (only)
- Adenoma heterogeneity

33. Schematic of normal mucosa through 2 alternative pathways to colorectal cancer, one via polypoid adenomas, the other via flat dysplasia

    [Emphasize that the flat dysplasia pathway is assumed to be minor.]

34. Schematic:
    normal epithelium---> small adenoma---> large adenoma--> invasive cancer

    [Recurrent adenomas represent neoplastic changes from normal mucosa through development of a small adenoma.
    Results of adenoma recurrence trials may be misleading if the intervention factor operates later in the neoplastic process, i.e., from small to large adenoma or large adenoma to cancer.
    A (false) null result for recurrent adenomas may result if the intervention operates only in the later stages of neoplasia.
    A positive result, though, suggests that cancer would be reduced, because large adenomas and cancers derive from small adenomas--inferential asymmetry.]

35. Schematic:
E1 + E2 ----> bad adenomas
E1 + E3 ----> innocent adenomas

[But here's a way by which adenoma findings might not be generalizable to cancer. Only a relatively small proportion of adenomas seem to go on to cancer. So you could postulate that adenomas are heterogeneous. One type, the bad adenomas, are caused by exposures 1 and 2-these go on to cancer. The second type, innocent adenomas, are caused by the same exposure 1 but in concert with exposure 3. Suppose our intervention works on 3. We could reduce the pool of innocent adenomas--thereby yielding a statistically significant reduction in adenoma formation in our trial--but in fact the incidence of bad adenomas and cancer would be unaffected. This could work the other way as well: see at most a small reduction in all adenomas even though the intervention affects bad adenomas and cancer.]

36. Diagram of CIN3 (cervical intraepithelial neoplasia type 3)

[Considered a strong surrogate for cancer. Used in large epidemiology studies, e.g., Mark Schiffman. Very high % will go on to cancer in 20 years (30-70%). Only very small fraction regresses. In fact, is very close to **being** invasive cancer.]

37. **Alternative Approaches to Adenoma Recurrence Trials**

- Eligibility = large/advanced adenoma [not all adenomas, as in current trials]
  - Rationale: field defect
  - Cost implications: screenees x 3 (so cost is up)
- End point = advanced adenoma (1 + cm, villous elements, high grade dysplasia) [not just all adenomas, as in current trials]
  - Rationale: reduced heterogeneity
  - Cost implications: recurrence x 1/6 (so cost is way up)

38. **Summary: Adenoma Recurrence as Surrogate End Point for Colorectal Cancer**

- Results of adenoma recurrence trials constitute strong--but not absolute--evidence regarding colorectal cancer.
- Adenoma recurrence trials are not inexpensive. Costs rise with alternative designs intended to strengthen inference.

39. **Surrogate End Points in Cancer Prevention Research: The 'No Free Lunch' Law***

Inferential certainty is directly associated with study cost.

***or, you get what you pay for**

This is just a hypothetical law: perhaps this workshop will demonstrate that the law is wrong, or operates only within certain contexts, e.g., cancer, but not for other diseases.

40. **Surrogate End Points in Cancer Prevention Research: Glass Half Empty or Half Full?**

- The limitations in using surrogate cancer end points need not be seen solely as a cause for pessimism...
- but also as an affirmation of the continued importance of large clinical trials (and observational epidemiologic studies) with explicit cancer end points.

41. Cartoon: Yesterday in this space I predicted that cancer would come to an end. It did not, however. I regret any inconvenience this may have caused.

But we do want to get things right....